**REMARKS**

The Claims

Claims 21-31 are pending in the application.

Rejection under 35 U.S.C. 103

Claims 21-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO97/23614 (Boyle et al., hereafter "Boyle") and further in view of WO98/28427 (Mann et al. hereafter "Mann"). The Examiner asserts that Boyle teaches Fc-OPG fusion proteins. Boyle is said to disclose that murine and human OPG have the same activity of decreasing bone resorption and share 90% sequence identity, and that amino acid residues 22-185 in OPG are required for activity. Mann is said to disclose an Fc protein of SEQ ID NO:1 in the present application and modifications thereof, as well as linkers that may be used to join an Fc protein to the protein of interest. The Examiner argues that it would have been *prima facie* obvious to substitute the human OPG protein for the murine OPG protein as taught by Boyle and produce a fusion protein with an Fc protein or a modified protein with a linker as allegedly taught by Mann et al. Moreover, the Examiner argues that addition of an Fc protein to the amino terminus of an OPG fragment or truncated polypeptide would be obvious because Boyle taught that murine OPG[22-194]-Fc had increased activity compared to murine OPG[22-194] alone, and the attachment of a polyethylene glycol (hereafter "PEG") molecule to the amino terminus of OPG[22-185] or [22-194] did not have an adverse effect on activity.

The results obtained with the presently claimed Fc-OPG fusion proteins are unexpected as there was no assurance that

addition of an Fc region to the amino terminus of an OPG polypeptide variant or fragment would enhance the activity of increasing bone density or decreasing bone resorption. By way of example, the *in vivo* activity of decreasing bone resorption by met-FcdC-OPG[22-194] as shown in Table 3 is greater than that for met OPG[22-194] which is shown in Table 2.
It was unexpected that such a result could have been obtained by constructing an Fc fusion to the amino terminal end of an OPG polypeptide variant or fragment.

Applicants maintain that the Examiner's arguments relating to the increased activity of OPG[22-194]-Fc compared to OPG[22-194] and the effects of PEG modifications of OPG[22-185] and OPF[22-194] do not support an obviousness rejection. One cannot assume that an increase in activity seen with a carboxy-terminal Fc fusion would also be observed when one made an amino terminal Fc fusion absent any information relating to amino terminal modifications of an OPG polypeptide fragment or variant by fusion to an Fc protein. Furthermore, an Fc-OPG fusion polypeptide represents a structurally distinct molecule from PEG-OPG wherein PEG is present on the amino terminus. Accordingly, there is no assurance that results obtained with PEG modification at the amino terminus can be extrapolated to Fc fusion at the amino terminus.

For these reasons, the obviousness rejection is not appropriate and should be withdrawn.

## CONCLUSION

Claims 21-31 are in condition for allowance and an early notice thereof is solicited.

Respectfully submitted,

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